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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,022	05/04/2001	Joseph D. Gold	091/005P	7806

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/849,022	GOLD ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,8,9,13 and 15-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,8,9,13 and 15-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 7/21/05 has been entered.

Applicants' Remarks and Amendment, filed 7/21/05 and 11/15/05, have been entered. Claims 8 and 9 have been amended; claims 1-3, 6, 8, 9, 13, 15-36 are pending and under current examination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 6, 8, 9, 13, 15-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 9, 15, 17, 19 of copending Application No. 11/010,140. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to obtaining differentiated cells from human ES cells. The instant claims are directed to methods of producing a population of genetically altered human ES cells and differentiating the genetically altered cells to differentiated cells, particularly neural cells or hepatocytes. The '140 claims are directed to methods of producing differentiated cells by isolating hES cells and genetically altering the cells before they are differentiated (see claim 1 and 9, for example). Specific embodiments of the '140 claims recite production of neural cells (claim 15), and hepatocytes (claim 17). Thus, the '140 claims render the instant claims obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-3, 6, 8, 9, 16-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 9, 10 of copending Application No. 10/141,220. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to differentiation of hES cells to neural cells or hepatocytes. The instant claims are directed to cells that are genetically altered and are then differentiated to neural cells or hepatocytes. The '220 claims are directed to a pair of isolate cell populations consisting of hES cells and a second cell population that is free of hES cells, but is the differentiated progeny of the hES cells. Paritcular embodiments teach genetically altering the second cell population (claim 2), wherein the second cell population is neurons or neural precursor cells (claim 9) or hepatocytes (claim 10). Thus, the '220 claims render the instant claims obvious

because they encompass producing the same cell types using the same starting material (hES cells).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6, 8, 9, 13, 15-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for :

1. Methods for producing a population of genetically altered pluripotent human ES (hES) cells comprising obtaining an undifferentiated population of hES cells essentially free of feeder cells, maintained in a culture environment that contains an extracellular matrix and fibroblast-conditioned medium, transfecting the pluripotent hES cells with a polynucleotide encoding a protein operably linked to an hES cell-specific promoter, maintaining the transfected, undifferentiated hES cells in a culture environment that contains an extracellular matrix and fibroblast-conditioned medium, thereby producing undifferentiated, genetically altered hES cells that express the protein while undifferentiated

2. Cell populations comprising undifferentiated hES cells, which are essentially free of feeder cells and cultured on an extracellular matrix in a medium conditioned by fibroblasts, wherein the population comprises cells expressing a protein from a heterologous polynucleotide, wherein the gene encoding the protein is operably linked to an hES cell-specific promoter, wherein the protein is expressed when the hES cells are undifferentiated.

3. Methods for producing genetically altered differentiated cells comprising a) obtaining a population of hES cells essentially free of feeder cells and maintained on an extracellular matrix in fibroblast-conditioned medium; b) transfecting the cells with a polynucleotide, thereby producing genetically altered cells; and c) causing the genetically altered cells to differentiate into a population of neurons or hepatocytes.

The specification does not reasonably provide enablement for the breadth of the claims, which recite that the population of hES cells are essentially free of feeder cells, but are not cultured in an environment containing both an extracellular matrix and fibroblast-conditioned medium; and cell populations which comprise any promoter other than an hES cell-specific promoter, methods of producing 50% neural cells under any conditions, methods of producing 50% hepatocytes under any conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is maintained for reasons of record advanced in the Office action, mailed 6/10/04.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that the claims have now been amended to recite that the hES cells are cultured essentially without feeder cells, but in a medium conditioned by fibroblast feeder cells. See p. 6 of the Response filed 7/21/05.

Response to Arguments. These arguments are considered, but not persuasive. The cell populations are not enabled for their full breadth, because they

encompass utilizing promoters that are not expressed only in ES cells. As stated in the Office action (mailed 6/10/04), Hamaguchi teaches that the PGK promoter (which is specifically recited in claims 24-26) is expressed in both mouse ES cells and differentiated cells. Similarly, specific embodiments contemplate utilizing EF1alpha promoter, however, a review of the art shows that EF1alpha is expressed in many tissues, including brain, placenta, lung, kidney and liver (see Entrez-Gene [online], retrieved, 2/6/06. Retrieved from the internet; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1915). Thus, the limitation that the genetically altered hES cells express the protein while undifferentiated is not enabled, because this protein would also be expressed when the cells are differentiated.

The methods to produce the genetically altered human ES cells are not enabling for specific reasons of record. In particular, as stated in the Office action mailed 6/10/04 (pages 5-6), the state of the art, with regard to culturing hES cells in an undifferentiated state is not found to be predictable. For example, the factors that are required by the hES cells to maintain them in an undifferentiated state have yet to be elucidated (see Lim *et al.*, cited previously). Furthermore, feeder cells are required for the maintenance of hES cells, as supported by the instantly-filed disclosure, which states that, "Without feeder cells in the culture environment, hPS cells soon die, or differentiate into a heterogeneous population of committed cells." See page 2, lines 7-8. Thus, given the unpredictable state of the art of maintaining human ES cells in an undifferentiated state, specific guidance must be provided in order to enable the claimed invention. Step a) of claim 1 recites obtaining a population of hES cells essentially free of feeder cells, in order for these cells to be undifferentiated, the cells would necessarily need to be cultured in specific conditions outlined by the teachings of the specification – in the presence of fibroblast-conditioned medium and an extracellular matrix. Furthermore, the claims, as broadly written, are not enabled, because they do not provide a

maintenance step for the resultant genetically modified hES cells. Although the claim recites that the hES cells would express the protein of interest while undifferentiated, there is no step in claim 1 that provides maintaining the cells with an extracellular matrix and fibroblast-conditioned medium.

With respect to claims 17-21, the breadth of the claims merely require differentiation of the hES cells to either hepatocytes or neural cells (see claim 17). One of skill in the art would recognize that hES cells had the capability to spontaneously differentiate into a variety of cell types, including hepatocytes or neural cells, as evidenced by teratoma formation (see p. 31, lines 17-23). However, specific embodiments of the claims require a certain percentage of either hepatocytes or neural cells. Example 2 teaches that the hES cells were induced to differentiate either by forming embryoid bodies or by direct differentiation. The resultant cells express neuron and cardiomyocyte markers (β-tubulin III and cardiac troponin I, respectively), see Figure 2. hES cells were directly differentiated by plating the cells onto glass cover slips that had been treated with poly-onithine, and the cells were then tested for neuron-specific markers and astrocyte-specific markers. The specification teaches that human ES cells produced 60-80% of cells containing *neurons*. There is no specific teaching of the percentage of cells that express astrocyte-specific markers. See p. 32, lines 1-7. Thus, the specification fails to teach that 50% neural cells (which encompass astrocytes, oligodendrocytes, neurons, etc.) would be able to be formed. The specification fails to provide specific teachings with regard to the generation of 50% hepatocytes. One of skill in the art would not be able to rely upon the state of the art to provide teachings with regard to the directed differentiation of hES cells to particular cell type, as encompassed by the claims. For example, Verfaillie *et al.* [**Hematology** (Am Soc Hematol Educ Program). 2002;:369-91] who review the state of the art of stem cells at the time of filing, teach, that, with regard to the directed differentiation of ES cells, "Many proposed applications of human ES cells are predicated on the assumption that it

will be possible to obtain pure populations of differentiated cells from the ES cultures. It might be envisioned that in order to achieve this one would treat ES cells with inducing agents that would convert them with high efficiency to a cell type of interest. In practice, that has not proven possible with the mouse system." See p. 278, 2nd column, Differentiation in vitro. Verfaillie teach that the ES cells can be treated with particular agents/factors that can drive differentiation along a specific lineage (see p. 379, 1st column, 1st full ¶. Verfaillie teach that spontaneous differentiation may be used in order to produce a wide variety of cell types through the formation of embryoid bodies (p. 378, 2nd column). They further show that, although specific cell types can be produced by differentiation of ES cells, specific steps must be provided. For example, they teach that neuronal differentiation is observed in ES cell aggregates, and these neuronal cells could be identified, selected and then transferred to a culture medium that supported neural stem cell growth in order to produce aggregates, which could subsequently be further differentiated to produce cells with the properties of mature neurons. See p. 379, 1st column, last ¶. The instant claims provide no specific steps to arrive at populations of 50% hepatocytes or neural cells. The guidance provided by the specification only teaches how to produce a population of 50% neurons, under specific conditions, which are not enabled by the breadth of the claims. Thus, given the teachings in the art and the guidance in the specification, it is clear that directed differentiation of ES cells to generate a particular cell type of interest is unpredictable.

Accordingly, in view of the state of the art with regard to the unpredictable state of maintaining hES cells in an undifferentiated state in the absence of fibroblast feeder cells, the specific guidance in the specification with regard to culturing hES cells in the presence of both an extracellular matrix and fibroblast-conditioned medium in the absence of feeder cells, the breadth of the claims, which encompass promoters that are expressed in differentiated and undifferentiated

cells, it would have required undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 recites the limitation "the composition" in step b) of the claim. There is insufficient antecedent basis for this limitation in the claim. The claim recites transfection of cells in "the composition". Step a) of the claim recites a population of hES cells, but does not recite a composition, therefore, it is unclear what "the composition" refers to. Claims 18-21 depend from claim 17.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 6, 8, 9, 16-18, 27, 28, 31, 32, 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reubinoff *et al.* (**U.S. Pat. No.**, 6,875,607 B1, issued April 5, 2005; filed November 9, 1999) when taken with Bodnar *et al.* (**WO 99/20740**, published April 29, 1999, Document AH of Applicants' IDS, filed 8/27/03).

The claims are directed to methods of producing a population of genetically altered human embryonic stem (hES) cells by obtaining a population of hES cells essentially free of feeder cells, transfecting the cells with a polynucleotide, while being cultured on an extracellular matrix in a medium conditioned by fibroblast feeder cells, wherein the polynucleotide comprises a protein encoding region operably linked to a promoter that promotes transcription of the encoding region while the cells are undifferentiated (claim 1). Specific embodiments are directed to preferentially selecting genetically altered cells (claim 2), maintaining the cells in the culture environment (claim 3); the polynucleotide is selected from an adenoviral vector, retroviral vector, a DNA plasmid complexed with a positively charged lipid (claim 6), cell populations comprising transfected, undifferentiated human ES cells, essentially free of feeder cells cultured on an extracellular matrix in a medium conditioned by fibroblast feeder cells (claims 8, 9), differentiating the hES cells (claim 16). The claims are directed to methods of differentiating genetically altered ES cells, by obtaining a population of hES cells, essentially free of feeder cells and maintained on an extracellular matrix in a medium conditioned by fibroblast feeder cells; transfecting at least some of the cells in the composition with a polynucleotide, thereby producing genetically altered cells; causing the cells to differentiate into a population of neural cells (claims 17-18). The claims are further directed to

populations of human cells (claims 27-28), and wherein the protein is a detectable, fluorescent label (claims 31-32), wherein the label is selected from luciferase or GFP (claim 33).

Reubinoff *et al.* teach human embryonic stem cells. They teach that cells are capable of differentiate spontaneous *in* vitro, and the cells stained positively for antibodies against neurofliament proteins and neural cell adhesion molecule (col. 21, lines 49-52) and, when injected into SCID mice, the tumors that formed showed various differentiated tissues, including primitive neuroectoderm and ganglionic structures (col. 22, lines 10-13 and Figure 6). They teach that the stem cells can identified by cell markers or by measuring the gene expression of genes specific to ES cells (such as Oct-4), or to particular cell lineages (col. 11, lines 62-66). They teach that cells can be sorted by using lineage-specific markers, including the use of FACS to isolate cells of interest (col. 6, lines 61-64, col. 14, lines 31-40). They teach that human ES cells can be modified at any stage of isolation, and can be modified by introduction of vectors expression a selectable marker that is under control of a stem cell-specific promoter, such as OCT-4. They teach that the differentiated products of the stem cells can produce gene products that are inhibitory to stem cell survival, and this system can be used to select for undifferentiated cells (col. 12, lines 8-22). They teach that the transfected ES cells can also be used to obtain differentiated cultures of somatic cells (col. 12, lines 37-47). They further teach that chemical differentiation may be used to induce differentiation (col. 13, lines 60-64). They teach that once the cells have been induced to differentiate, they can then be separated and selectively cultivated. The hES cells can be induced to differentiate into neuronal cells in high density culture, and then can be isolated and replated (col. 14, lines 50-56).

Reubinoff *et al.* do not teach culturing the hES cells in a culture environment that is essentially free of feeder cells, in the presence of an extracellular matrix, and in a medium conditioned by fibroblast feeder cells. However, prior to the time the

claimed invention was made, Bodnar *et al.* teach methods of maintaining primate-derived primordial stem cells in an undifferentiated state by culturing them in a cell culture medium and an extracellular matrix. They teach that a conditioned medium is one that is supplemented with soluble factors derived from feeder cells (page 5, #3.1.2); they teach that feeder cells include mouse embryonic fibroblasts and STO cells (p. 10, lines 1-3) and the extracellular matrix can be derived from these feeder cells (p. 10, line 4). They teach that the primate-derived primordial stem cells can be cultured in feeder-free conditions, using a conditioned medium, and in the presence of a matrix (p. 11, lines 19-24). They further teach that the stem cells can be genetically modified, using methods, such as utilizing a positive-negative selection vector, or any of those known in the art (p. 16, lines 12-21).

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art to modify the culture conditions, as taught by Reubinoff *et al.* to conditions which include an extracellular matrix and fibroblast-conditioned medium, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make these modifications in order to reduce potential contamination from any viruses that might be present in the mouse feeder cells, and optimize culture conditions, and as Bodnar states, "[C]urrent methods of culturing primate-derived primordial stem cells require a feeder layer that complicates and slows the process of cell cultivation."

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 13, 22, 23, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reubinoff *et al.* when taken with Bodnar *et al.* as applied to claims 1-3, 6, 8, 9, 16-18, 27, 28, 31, 32, 33 above, and further in view of Capecchi *et al.* (**U.S. Pat. No.**, 5,464,764, November 7, 1995).

Reubinoff *et al.* and Bodnar *et al.* are detailed above. They do not teach or suggest that at least 90% of the undifferentiated cells have been genetically altered (claim 9), the polynucleotide encodes a drug resistance gene (claim 22), selecting the cells in the presence of a drug to which the transfected cells are resistant (claim 23), wherein the protein is a factor that supports the growth of hES cells (claim 29). Bodnar *et al.* generally contemplate genetically modified embryonic stem cells, and particularly contemplate using a positive-negative selection vector, as described in Capecchi *et al.* (see p. 16, lines 15). Capecchi *et al.* teach a positive-negative selector vector tomodify a target DNA sequence by homologous recombination. Particularly, the vector contains both a positive and negative selection marker in order to identify cells that have been transfected with the construct. In particular, they teach the positive selection comprises contacting cells infected with these vectors, and selecting for cells that do not contain the selection marker. They also teach that negative selection comprises contacting the cells with a particular agent, and cells that are transfected with the vector are killed. See col. 7, lines 29-45. They particularly teach selectable markers that can be used, including drug resistance genes (for example *Neomycin*), See Table I.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art to modify the teachings of Reubinoff *et al.* and Bodnar *et al.* (as taught above), to produce cells that are at least 90% transfected (by positive selection), to produce ES cells that have a drug resistance gene (such as *neomycin*), to select for cells that are transfected (by positive selection), and expression of this positive selection marker supports the growth of the hES cells, in the presence of the selection agent, as taught by Capecchi *et al.*, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification, as Bodnar *et al.* contemplate utilizing Capecchi's methods, and further, teach that utilizing these vectors would provide

for an efficient methodology to modify and select for transfected ES cells (see col. 15-16, bridging ¶).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 34, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reubinoff *et al.* when taken with Bodnar *et al.* as applied to claims 1-3, 6, 8, 9, 16-18, 27, 28, 31, 32, 33 above, in further view of Gerson *et al.* (U.S. Pat. No. **5,591,625**, January 7, 1997).

Reubinoff *et al.* and Bodnar *et al.* are detailed above. They do not specifically teach that the protein is a detectable label, that it is a cell surface protein detectable by antibody staining (claim 34), the label is an enzyme, and is selected from alkaline phosphatase, β-galactosidase, neophosphotransferase (claims 35-36). Bodnar *et al.* generally contemplate genetically modified embryonic stem cells, and specifically contemplate using the methods taught by Gerson *et al.* to produce cells that have augmented expression of certain gene products and cell surface proteins (see page 16, lines 21-24). Gerson *et al.* specifically teach transduction of mesenchymal stem cells with particular gene products, including cell surface proteins (claim 34). They particularly teach using constructs with LacZ (see Figure 2, for example).

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art to modify the teachings of Reubinoff *et al.* and Bodnar *et al.* (as taught above), to produce ES cells with a detectable label, particularly lacZ, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make these modifications, as Bodnar *et al.* contemplate using these methods, for screening for specific, introduced genetic modifications.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

thaian ton

Thaian N. Ton
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